# Psychological correlates of fatigue in Rheumatoid Arthritis: A systematic review

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**Abstract**

Fatigue is common and debilitating in Rheumatoid Arthritis (RA). A focus on the psychological variables associated with fatigue may help to identify targets for intervention which could enhance the treatment of fatigue in RA. The purpose of this review was to systematically identify psychological variables related to fatigue in RA, with the overall aim of suggesting evidence-based targets for fatigue intervention in RA. Twenty-nine studies met inclusion criteria and were included in the narrative synthesis. A wide range of psychological variables were addressed, spanning 6 categories: affect and common mental disorders; RA-related cognitions; non-RA-related cognitions; personality traits; stress and coping; and social support/interpersonal relationships. The most consistent relationship was found between mood and fatigue, with low mood frequently associated with increased fatigue. Some evidence also highlighted the relationship between RA-related cognitions (such as RA self-efficacy) and fatigue, and non-RA-cognitions (such as goal ownership) and fatigue. Limited evidence was found to support the relationship between stress and coping or personality traits and fatigue, although mixed evidence was found for the relationship between social support and fatigue. The results of this review suggest the interventions for fatigue in RA may benefit from a focus on mental health, and disease-related cognitions.

**Keywords:** fatigue, Rheumatoid Arthritis, psychological, mood, cognitions, social support, stress, coping, personality, intervention, systematic review.

# Introduction

Rheumatoid Arthritis (RA) is a chronic autoimmune disease which affects 0.2-1.2% of the adult population (Alamanos, Voulgari, & Drosos, 2006). RA is progressive and primarily affects the joints, leading to increased pain, functional disability and joint destruction (Kvien, 2004). In addition to the impact RA has on joints and physical disability, there are other extra-articular manifestations which can also contribute to poor patient outcomes. RA significantly impacts quality of life, with RA patients showing notably lower fatigue-related quality-of-life in comparison to the general population (Matcham et al., 2014). Fatigue is reported in over 80% of RA patients (Belza, Henke, Yelin, Epstein, & Gilliss, 1993; Belza, 1995; Pollard, Choy, Gonzalez, Khoshaba, & Scott, 2006). More conservative estimates are still high: approximately 40% of RA patients experience persistent fatigue over one year (Repping-Wuts, Fransen, Van Achteberg, Bleijenberg, & Van Riel, 2007) and 57% of RA patients identify fatigue as the most problematic symptom of their condition (Wolfe, Hawley & Wilson 1996).

Fatigue is often experienced in healthy people (Pawlikowska, Chalder, Hirsch, Wallace, Wright, & Wessely, 1994); it is usually transient and can be caused by a lack of sleep or high stress levels (Loge, Ekeberg, & Kaasa, 1998). In the general population, fatigue is a universal symptom, existing on a spectrum of severity and chronicity, at one end of which patients have persistent fatigue, contributing to substantial impairment. Qualitative studies have revealed that despite fatigue being the most problematic symptom for the majority of patients with RA, patients' experiences are that this is often dismissed by healthcare professionals (Hewlett et al., 2005). Furthermore, despite the high prevalence of fatigue in RA, and the clear impact fatigue has on patients' well-being, fatigue is infrequently reported in RA trials (Kalyoncu, Dougados, Daurès, & Gossec, 2009). Fatigue in RA tends to be chronic and is associated with increased levels of pain and depression, and reduced functional status and quality-of-life (Rupp, Boshuizen, Jacobi, Dinant, & van den Bos, 2004; Mayoux-Benhamou 2006; van Hoogmoed, Fransen, Bleijenberg, & van Riel, 2010).

A recent review examining variables relating to fatigue in RA found that the most consistent relationships were between fatigue and pain, disability and depression (Nikolaus, Bode, Taal, & van de Laar, 2013). Whilst this review examined a broad range of variables relating to fatigue, there was limited focus on social and behavioural variables. In their guidelines for the for management of early rheumatoid arthritis, Luqmani et al. (2006) report that the strong

associations between fatigue and reduced quality-of-life and increased work dysfunction highlight a need for further research establishing the course of fatigue in RA and developing effective treatment strategies for fatigue management.

Meta-analysis evidence suggest that biotherapies have small-to-moderate effects on fatigue outcomes (Chauffier, Salliot, Berenbaum, & Sellam, 2012). This systematic review found an overall effect size of 0.45 (95%CI: 0.31-0.58) when comparing all disease modifying RA drugs with placebo. There is currently no systematic review examining the impact of other pharmacological interventions (such as antidepressants) on fatigue outcomes in RA. Psychological factors may also be help to identify patients at risk of reduced fatigue biotherapy response (Druce, Jones, Macfarlane, & Basu, 2014). A focus on the psychological variables associated with fatigue may be crucial not only for developing psychological interventions for fatigue, but also for identifying patients who may not benefit from traditional biotherapy for fatigue.

There is some evidence to suggest that psychological interventions may improve fatigue outcomes (Hewlett et al., 2011a; Cramp et al., 2013). A conceptual, dynamic model of fatigue incorporating disease-related factors (such as inflammation and medication), personal factors (social support and work environment), and cognitive behavioural factors (including thoughts and feelings), has been developed (Hewlett et al., 2011b). However in comparison to other physical conditions, there has been limited systematic assessment of the psychological variables associated with fatigue in RA, and until such a review is conducted, the most useful target variables for intervention in this population remain unknown.

The aim of this review is to identify studies assessing psychological factors which may be associated with, predict or explain fatigue outcomes in RA. The aims are: a) to ascertain the strength of evidence for relationships between psychological variables and fatigue in RA; b) to map identified psychological variables onto commonly used models of chronic fatigue, in an attempt to clarify the most useful target variables for interventions; and c) to identify methodological issues and gaps in literature the with the aim to advise the direction of future research. For the purposes of this review, psychological factors are defined as variables which relate to behaviours, feelings, thoughts and attitudes which would be modifiable for the purposes of intervention, or which may moderate the effects of treatment.

# Method

## *Search Strategy and Selection Criteria*

The systematic review protocol and data extraction forms were designed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Moher, Liberati, Tetzlaff, & Altman, 2009). Electronic databases (PsychINFO, Web of Science, MEDLINE, EMBASE, CINAHL) were systematically searched from inception to March 2013, using customised search terms for each database. Search terms involved combining key word searches for fatigue ("Fatigue" or "tiredness"), the terms "determine$", "predict$" or correlate$", and "Rheum*" or "Rheumatoid Arthritis".

## *Inclusion and Exclusion Criteria*

Included studies met the following criteria: (i) observational design, or baseline cross-sectional data from a trial; (ii) published quantitative studies examining psychological factors relating to fatigue in RA; (iii) reported results for RA separately from other rheumatological conditions.

Studies were excluded if they: (i) used qualitative, case-series, case-reports, expert opinion or consensus statements; (ii) used a selective sample (e.g., intervention trials); (iii) did not use published/appropriate and replicable measures to assess psychological factors and fatigue; (iv) did not report fatigue as the outcome variable in a regression analysis; (v) recruited patients with self-reported RA diagnosis. Where multiple publications came from the same group of researchers and same patient group, data were retained for uniquely assessed psychological variables. That is, if two studies represented the same patient group and one examined fatigue and depression, and the other examined fatigue and social support, then data from both papers were included. To increase the external validity of our results, studies using selective samples (interventions and randomised controlled trials) were excluded. These designs typically stipulate rigorous eligibility criteria (such as limited comorbidities and high disease activity), which may limit the generalizability of their results to the general RA patient population (Rothwell, 2005).

A post-hoc decision was made to exclude studies measuring quality-of-life (QoL) in relation to fatigue, as QoL was not deemed a modifiable psychological variable. However due to the

content similarities between the Mental Health subscale of the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36, a measure of general QoL; Ware & Sherbourne, 1992) and other validated mental health screening tools, it was decided that studies reporting associations between mental health QoL would be included as potentially modifiable psychological constructs.

## *Data Extraction*

Study titles then abstracts were screened by two research assistants, in collaboration with one researcher (FM). The full texts were then screened by FM and all ineligible papers were excluded. Information from each eligible study was extracted and tabulated. Extracted data included country of origin, study design, data analysis methodology, sample characteristics, relevant measures, main findings, and aspects of methodology quality. The extraction process was completed independently by two researchers, FM and SA, and any disagreements resolved through discussion of the study with TC. Where only abstracts were available, or insufficient information was reported, authors were contacted via email. Only one paper was excluded due to insufficient information being reported and the author remaining un-contactable (Figure 1).

## *Data Synthesis*

The heterogeneity of the included studies and broad nature of the review aim precluded meta-analysis.

Psychological variables were grouped into overarching categories, representing conceptually or thematically comparable constructs. A box-score method was used to quantify the relationships between the identified psychological variables and fatigue. This method involves tabulating each variables and its relationship with fatigue, in terms of significance and direction: a positive sign (+) was given for a positive significant association between variables; a negative sign (-) for a negative significant association between variables; and a nought (0) for no association between variables (Green & Hall, 1984). This table also takes into account the study design (cross-sectional or longitudinal) and level of analysis (bivariate or multivariate). Thus tabulated associations could be synthesised alongside indicators of study quality. Data from all analyses are included in the box-score table, meaning that data from both bivariate and multivariate models are included, in order to retain as much data for comparison as possible.

Elements of study quality were also assessed, selected from a previously used quality-assessment tool (Matcham et al., 2013), to be applicable for both cross-sectional and longitudinal study designs. These included: whether the psychological variable of interest was measured using a validated tool; whether fatigue was measured using a multi-item questionnaire (as opposed to a VAS); whether the recruitment strategy was randomised/consecutive; whether the participants were recruited from multiple centres (representing multiple locations, not just multiple centres within the same city, for example); whether eligibility criteria were specified; whether participation rate was greater than 75%; whether the study was adequately powered. Where studies did not report anything for a particular eligibility indicator, they were allocated to the "No" category.

# Results

In the following results section, we present the following information:

1. Results of the systematic search and characteristics of included studies.
2. Description of the identified psychological variables and allocation into categories.
3. Affect and common mental disorder
4. RA-related cognitions
5. Non-Ra-related cognitions
6. Personality Traits
7. Stress and Coping
8. Social Support and Interpersonal relationships

## *Search Results/Study Characteristics*

The literature search yielded 3,387 relevant articles (Figure 1). Removal of duplicates, title and abstract screening left 218 articles for full-text screening. One hundred and eighty nine of these did not meet our eligibility criteria. The most common reason for exclusion was for not having measured or reported eligible psychological variables. Twenty-nine studies were deemed eligible for inclusion in the narrative synthesis.

Figure 1. Flow chart of the selection of relevant studies

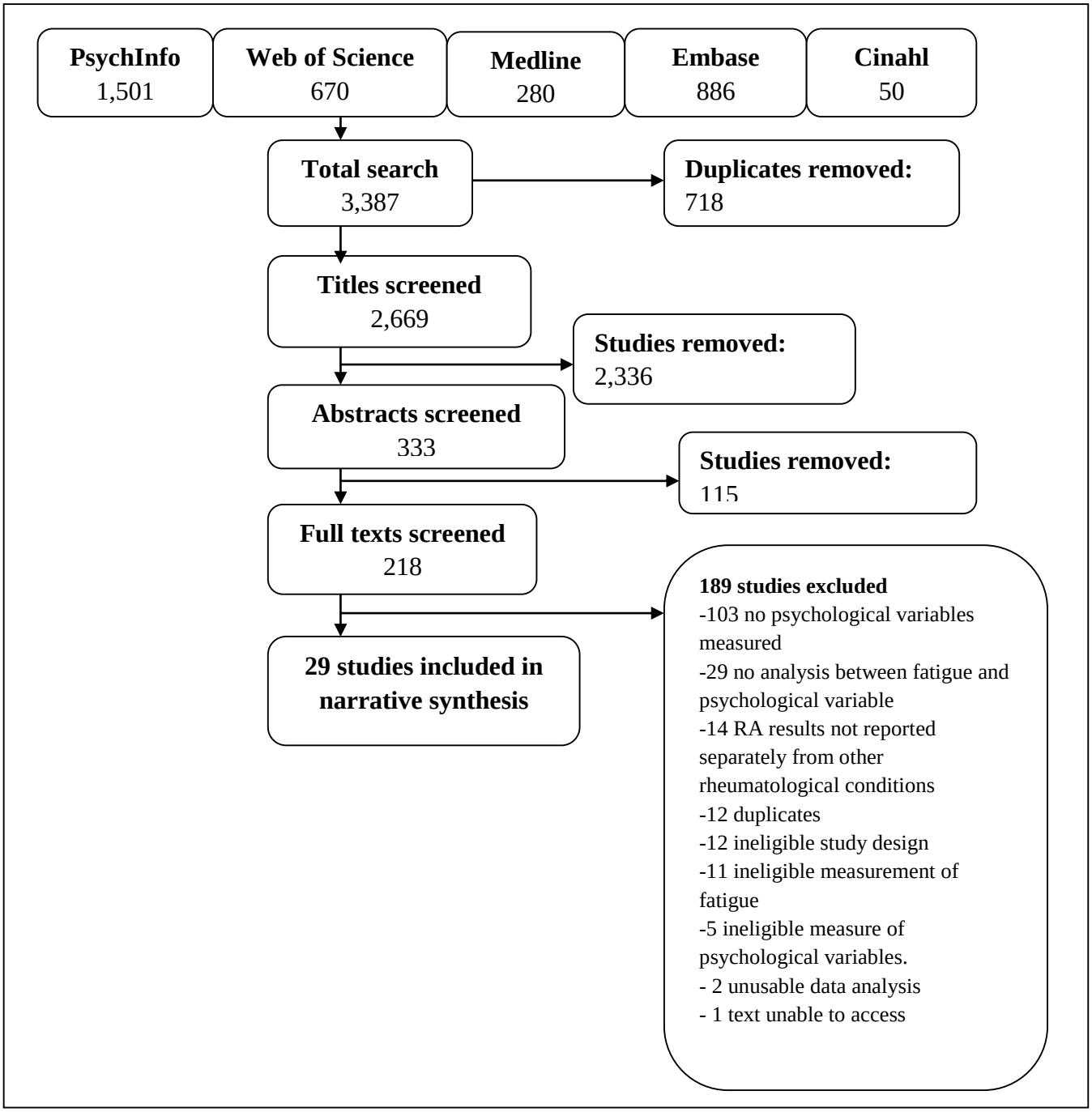

**Table 1. Studies included in narrative synthesis**

| Author, year (ref.) | Sample (country, population, gender) | Setting, recruitment strategy | Study Design, analysis method | Fatigue measurement | Psychological variables |
|---|---|---|---|---|---|
| Barlow 2002 | UK,<br>N = 60,<br>Mean age: 59.2 (11.3)<br>86.7% female<br>Mean disease duration (years): 16.9 (13.7) | Rheumatology outpatients, consecutive recruitment | Longitudinal, Pearson's product moment. | VAS, 100mm horizontal line anchored 0 (no fatigue) and 10 (fatigue as bad as it could be). | Depression (HADS)<br>Anxiety (HADS)<br>Illness acceptance (AIS)<br>Self-efficacy (ASES)<br>Positive affect (PANAS)<br>Negative affect (PANAS) |
| Belza 1993 | USA,<br>N = 133,<br>Mean age: 67.0 (6.6)<br>75.0% female<br>Mean disease duration (years): 18.0 (10.5) | Arthritis Research Centre, "selected" | Cross-sectional, hierarchical multiple regression analysis | MAF | Depression (GDS)<br>Arthritis Helplessness (AHI) |
| Belza 1995 | USA,<br>N = 51,<br>Mean age: 43.6 (8.9)<br>75.0% female<br>Mean disease duration (years): 10.7 (8.3) | Rheumatology outpatients, recruitment strategy NS | Longitudinal, Pearson's correlation | MAF | Depressed mood (POMS) |
| Brekke 2003 | Norway,<br>N = 306,<br>Mean age: 53.3 (11.4)<br>80.4% female<br>Mean disease duration (years): 11.0 (9.3) | Oslo RA register | Longitudinal, Pearson's correlation | VAS, 100mm horizontal line anchored 0 (no fatigue) and 10 (fatigue as bad as it could be). | Self-efficacy (ASES)<br>Affect (AIMS2)<br>Mental Health (SF-36) |

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|---|---|---|---|---|---|
| Covic 2006 | Australia,<br>N = 134,<br>Mean age: 58.5 (11.9)<br>77.0% female<br>Mean disease duration (years): 13.2 (9.5) | Rheumatology clinics, convenience sampling | Cross-sectional, discriminant analysis | VAS, 100mm horizontal line anchored 0 (no fatigue) and 10 (fatigue as bad as it could be). | Depression (CESD) |
| Cross 2008 | Australia,<br>N = 52,<br>Mean age: 65.5 (12.4)<br>79.0% female<br>Mean disease duration (years): 26.0 (10.8) | Rheumatology outpatients, convenience sampling | Cross-sectional, Spearman correlations, regression analysis | FSS, MAF | Self-efficacy (ASES)<br>Mental Health (SF-36) |
| Davis 2010 | USA,<br>N = 228,<br>Mean age: 55.3 (13.2)<br>69.3% female<br>Mean disease duration (years): 13.4 (13.1) | Advertising, convenience sampling | Follow-up, multi-level modelling | VAS, 0 (no fatigue) to 100 (fatigue as bad as it can be). | Daily interpersonal events (daily diaries, ISLE)<br>Positive affect (PANAS)<br>Negative affect (PANAS) |
| Fifield 1998 | USA,<br>N = 227,<br>Mean age: 55.5 (10.0)<br>78.0% female<br>Mean disease duration (years): 17.0 (8.0) | National Rheumatoid Arthritis Panel study, "selected" | Cohort, ANOVA | VAS, 0 (no fatigue) to 100 (fatigue as bad as it can be). | Depression (DIS for DSM-III)<br>Dysphoria (CESD) |

| | | | | | |
|---|---|---|---|---|---|
| Huyser 1998 | USA,<br>N = 73,<br>Mean age: 59.3 (10.6)<br>54.8% female<br>Mean disease duration (years): 12.9 (9.7) | Longitudinal study, convenience sampling | Cross-sectional, Spearman correlations, best regression model derivation | Piper Fatigue Scale | Self-efficacy (ASES)<br>Arthritis impact (AIMS)<br>Depressed mood (CESD)<br>Psychological distress (SCL-90)<br>Stress (DSI)<br>Hassles (HS)<br>Anxiety (STAI)<br>Coping (CSQ) |
| Ibn Yacoub 2012 | Morocco,<br>N = 248,<br>Mean age: 47.5 (79.0)<br>79.0% female<br>Mean disease duration (years): 10.6 (8.1) | Rheumatology outpatients, recruitment strategy NS | Cross-sectional, Pearson's correlation, multiple linear regression model | VAS, 100mm horizontal line anchored 0 (no fatigue) and 10 (worst fatigue imaginable). | Mental Health (SF-36) |
| Jump 2004 | USA,<br>N = 122<br>Mean age: 59.9 (9.7)<br>92.6% female<br>Mean disease duration (years): 21.0 (8.3) | National Rheumatoid Arthritis Panel study, "selected" | Cohort, Pearson's correlation. | MAF, GFI | History of mood disorder (depression/anxiety) (DSM-IV)<br>Neuroticism (NEO)<br>Self-efficacy (ASES) |
| Maes 2012 | The Netherlands,<br>N = 129, | NS | Longitudinal, hierarchical regression analysis | CIS-20 | Goal ownership (TSRQ)<br>Self-efficacy (SRSB) |

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|---|---|---|---|---|---|
| Mancuso 2006 | USA,<br>N = 122,<br>Mean age: 49.0 (12.0)<br>84.0% female | Rheumatology practices, recruitment strategy NS | Cross-sectional, multivariate regression analysis | FSS | Anxiety (STAI)<br>Depression (GDS)<br>Social support/social stress (DSSS)<br>Role satisfaction (Likert scale 1-5) |
| Neame 2005 | UK,<br>N = 344,<br>67.0% female<br>Median disease duration (years): 13.3 (6.0-25.0) | DMARD monitoring database, "selected" | Cross-sectional, Bivariate, partial correlations | VAS | Beliefs about medications (BMQ)<br>Psychological distress (VAS) Attitudes (RAI) |
| Nicklin 2010 | UK,<br>N = 229,<br>76.4% female | Rheumatology outpatients, consecutive recruitment | Cross-sectional, Spearman correlations | BRAF, FACIT-F, MAF, POMS, SF-36 | Depression (HADS)<br>Anxiety (HADS)<br>Helplessness (AHI) |
| Pollard 2006 | UK,<br>N = 274,<br>Mean age: 64.0<br>Mean disease duration (years): 12.0 | Rheumatology outpatients, recruitment strategy NS | Cross-sectional, multiple regression | VAS, 100mm horizontal line | Mental Health (SF-36) |
| Rezvani 2012 | Turkey,<br>N = 50,<br>Mean age: 50.6 (8.9)<br>90% female<br>Mean disease duration (years): 9.2 (6.0) | NS | Cross-sectional, correlation analysis | VAS | Depression (HADS)<br>Anxiety (HADS)<br>Illness Perceptions (BIPQ) |

| | | | | | |
|---|---|---|---|---|---|
| Riemsma 1998 | The Netherlands,<br>N = 229,<br>Mean age: 63.3 (11.7)<br>61.0% female<br>Mean disease duration (years): 18.7 (10.6) | Rheumatology outpatients, consecutive recruitment | Cross-sectional, linear regression | VAS | Affect (AIMS)<br>Social Support (SSLI2-I)<br>Self Efficacy (ASES)<br>Self-efficacy expectations (SMS) |
| Rupp 2004 | The Netherlands,<br>N = 400,<br>Mean age: 60.7 (13.4)<br>72.7% female<br>Mean disease duration (years): 10.7 (9.2) | Rheumatology outpatients, recruitment strategy NS | Cross-sectional, Spearman's correlation | VAS, MFI | Depression (CESD) |
| Stebbings 2010 | New Zealand,<br>N = 103,<br>Mean age: 58.4 (12.2)<br>70.9% female<br>Mean disease duration (years): 14.8 (12.7) | Rheumatology outpatients, consecutive recruitment | Cross-sectional, linear regression | MAF | Depression (HADS)<br>Anxiety (HADS) |
| Stone 1997 | USA,<br>N = 35,<br>Mean age: 52.4 (12.3)<br>71.4% female | Rheumatology practices, convenience sampling | Follow-up, OLS regression, RMANOVA | Ecological Momentary Assessment | Anxiety (STAI) |
| Thyberg 2009 | Sweden,<br>N = 276,<br>Mean age: 54.0 (14.0)<br>69.2% female | Multi-centre project, randomised sampling | Longitudinal, multiple linear regression | VAS | Mental Health (SF-36) |

| | | | | | |
|---|---|---|---|---|---|
| Treharne 2005 | UK,<br>N=154<br>Mean age = 56.3 (15.1)<br>73.0% female | Rheumatology outpatients, recruitment strategy NS | Cross-sectional, correlation analysis | VAS | RA control/cure (IPQ)<br>Beliefs about medications (BMQ)<br>Optimism/Pessimism (LOT)<br>Self-Consciousness (SCS)<br>Social Support (SSS)<br>Anxiety (HADS) |
| Treharne 2007 | UK,<br>N = 129,<br>Mean age: 55.4 (14.3)<br>75.0% female | Rheumatology outpatients, consecutive recruitment | Cross-sectional, Spearman's correlation | VAS | Perceived stress (PSS) |
| Treharne 2008 | UK,<br>N = 114,<br>Mean age: 55.8 (14.5)<br>73.7% female | Rheumatology outpatients, recruitment strategy NS | Longitudinal, hierarchical linear regression | VAS, 100mm horizontal line anchored "no fatigue" and "unbearable fatigue". | Depression (HADS)<br>RA consequences (IPQ)<br>Self-Efficacy (ASES)<br>Coping (CSQ) |
| van Hoogmoed 2012 | The Netherlands,<br>N = 228,<br>Mean age: 55.9 (10.8)<br>63.0% female<br>Median disease duration (years): 10.0 (6-17) | Rheumatology outpatients, recruitment strategy NS | Cross-sectional, backward multiple regression | CIS-20 | Depression (BDI-pc)<br>Psychological Distress (SCL-90)<br>Mental Health (SF-36)<br>Self-esteem (RSE)<br>Optimism (LOT)<br>Attributions (CAL)<br>Self-efficacy (SES-28)<br>Coping (MPCI)<br>Catastrophising (FCS) |

| | | | | | |
|---|---|---|---|---|---|
| Waltz 2000 | Germany & The Netherlands,<br>N = 234,<br>Mean age: 58.5<br>69.0% female<br>Median disease duration (years): 10.0 | Rheumatology outpatients, consecutive recruitment | Longitudinal, correlation anlysis | CFIF | Depression (CESD) |
| Wolfe 1996 | USA,<br>N = 628,<br>Mean age: 61.9<br>74.7% female<br>Median disease duration (years): 10.0 (6.5-17.9) | Rheumatology outpatients, consecutive recruitment | Cross-sectional, multivariate regression analysis | VAS, anchored "fatigue is no problem" and "fatigue is a major problem". | Anxious mood (AIMS)<br>Depressed mood (AIMS) |
| Wolfe 2004 | USA,<br>N = 21,076,<br>Mean age: 54.6 (11.4)<br>79.7% female<br>Mean disease duration (years): 13.7 | Data bank | Cross-sectional, multiple regression | VAS, anchored "fatigue is no problem" and "fatigue is a major problem". | Anxious mood (AIMS)<br>Depressed mood (AIMS) |

NS = Not Stated; VAS = visual analogue scale; HADS = Hospital Anxiety and Depression Scale; AIS = Arthritis Illness Acceptance Scale; ASES = Arthritis Self-Efficacy Scale; PANAS = Positive and Negative Affect Scale; MAF = Multi-Dimensional Assessment of Fatigue; GDS = Geriatric Depression Scale; AHI = Arthritis Helplessness Index; POMS = Profile of Mood States; AIMS2 = Arthritis Impact Scale 2; SF-36 = Medical Outcomes Study 36-item Short-Form Health Survey; CESD = Centre for Epidemiological Studies Depression Scale; FSS = Fatigue Severity Scale; ISLE = Inventory of Stressful Life Events; DIS = Diagnostic Interview Schedule; DSM-II = Diagnostic and Statistical Manual III; SCL-90 = 90-item symptom checklist; DSI = Daily Stress Inventory; HS = Hassles Scale; STAI = State Trait Anxiety Inventory; CSQ = Coping Strategies Questionnaire; ANOVA = Analysis of Variance; TSRQ = Treatment Self-Regulation Questionnaire; SRSB = Self-regulation Skills Battery; CIS-20 = Checklist Individual Strength; DSSSS = Duke Social Support and Stress Scale; BMQ = Beliefs about Medications Questionnaire; RAI = Rheumatology Attitudes Index; BRAF = Bristol Rheumatoid Arthritis Fatigue; FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue; (B)IPQ = (Brief) Illness Perceptions Questionnaire; BDI-pc = Beck Depression Inventory for Primary Care; RSE = Rosenberg Self-Esteem scale; LOT = Life Orientation Test; CAL = Causal Attribution List; SES-28 = Self-Efficacy Scale-28; MPCI-F = Modified Pain Coping Inventory for Fatigue; FCS = Fatigue Catastrophising Scale.

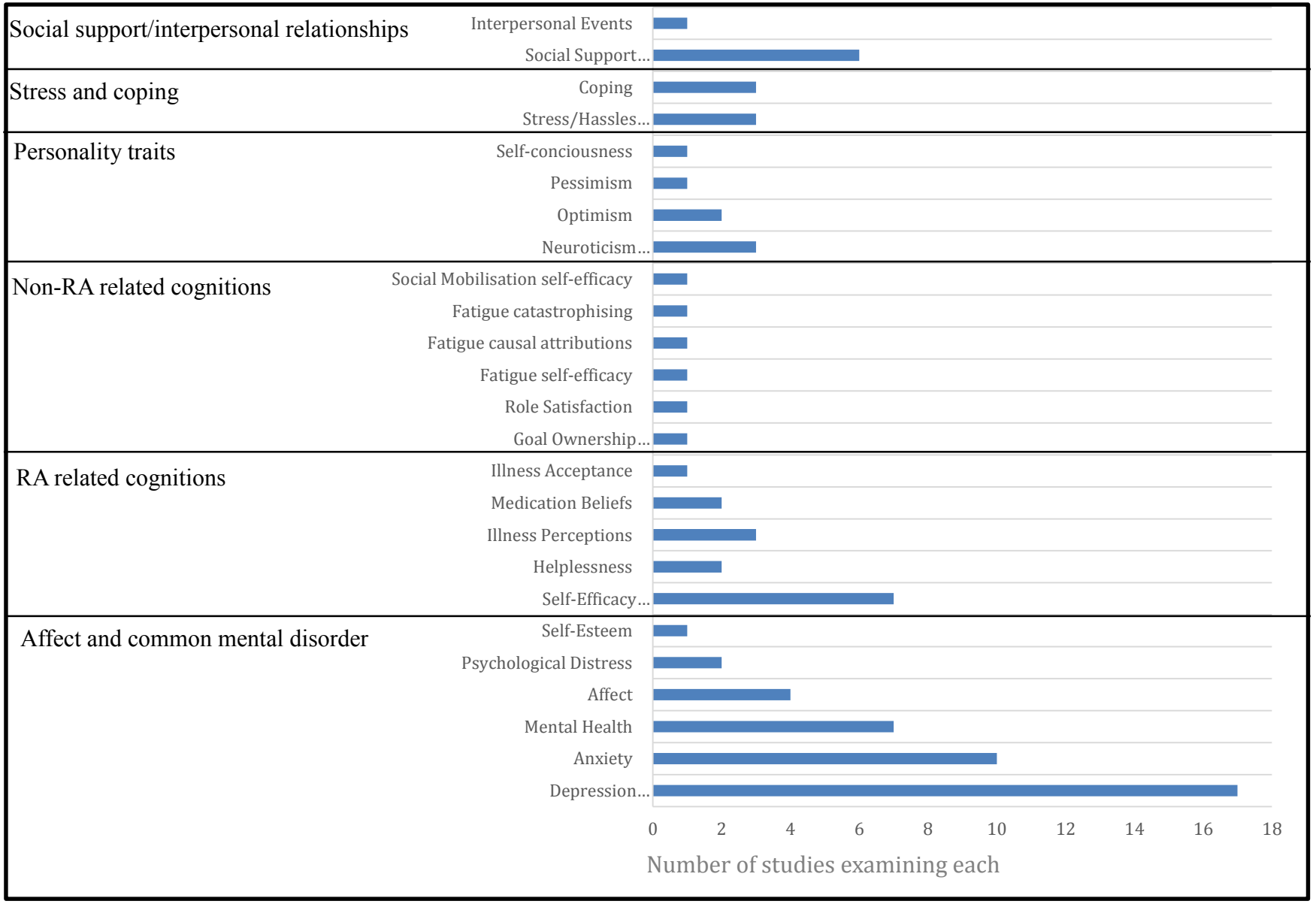
Table 1 presents the 29 studies included in the review. The most common method of measuring fatigue was through visual analogue scale (VAS), used by 17 (58.6%) studies. The Multidimensional Assessment of Fatigue (MAF; Neuberger, 2003) was the second most frequently used tool, used by 5 (17.2%) studies. The studies represented 26,388 individuals with RA. Sample sizes ranged from 35 to 21,076, and the median sample size was 154 (interquartile range (IQR) = 114-248). The median of mean age was 56 (IQR = 53-59). The median percentage of females represented in the sample was 75% (IQR= 69%-79 %). The median of mean disease duration was 13.4 years (IQR= 11.0 years – 17.0 years), and the most frequent setting for patient recruitment was outpatient clinics, with 18 (62.1%) studies recruiting from them. Only 17 (58.6%) reported a recruitment strategy, and only eight (27.6%) used a random or consecutive recruitment strategy.

## *Identified Psychological Variables*

A summary of the psychological variables identified and the number of studies examining each variable is shown in figure 2. In total, 25 different psychological variables were examined, which were categorised into six broad categories. Affect and common mental disorder included mental health-related variables, incorporating both identification of depression/anxiety disorders via validated screening tools or diagnostic interview, as well as more generalised elements of psychological distress, mental health, affect and self-esteem. Depression (N=17) was most commonly reported, with anxiety (N=10) being the second most commonly reported variable from this category.

RA-related cognitions included variables such as self-efficacy, arthritis helplessness, illness perceptions, medication beliefs and illness acceptance. Disease self-efficacy was the most commonly-reported variable (N=8), followed by illness perceptions (N=3). Non-RA related cognitions were defined as variables which were related to cognitive processes unrelated to having a physical illness. This category included other types of self-efficacy (social-mobilisation and fatigue-related), as well as role satisfaction, goal ownership, catastrophizing and fatigue attributions. Neuroticism was the most commonly assessed personality trait (N=3), and stress and coping mechanisms were included in a stress and coping category. Finally, the social support and interpersonal relationships category contained data relating to social mechanisms.

Figure 2. Graph of identified psychological variables.



## Table 2. Box analysis of psychological variables examined in relation to fatigue.

Variables associated with fatigue outcomes in RA.

| Category | Factor | | Cross-sectional | | Longitudinal/follow-up | |
|---|---|---|---|---|---|---|
| | | | Bivariate | Multivariate | Bivariate | Multivariate |
| Affect and common mental disorder | Depression | | +,+,+,+,+,+,+,+,+,+,+,+,+,+,+,+? | 0,0,+,+,+,+ | 0,+ | 0,0,0 |
| | Anxiety | | +,+,+,+,+,+,+,+,+ | 0,0,0 | + | +,0 |
| | Mental Health | | -,-,-,- | 0,0,- | -,- | - |
| | Psychological Distress | | + | + | | |
| | Affect | | 0,+ | 0,0 | + | |
| | Self-Esteem | | - | 0 | | |
| RA-related cognitions | Self-Efficacy | Pain | - | | | |
| | | Other symptoms | -,- | 0 | + | + |
| | | General | -,- | -,- | | |
| | | Function | - | 0 | | |
| | | Coping with RA | - | - | | |
| | Helplessness | | + | 0 | | |
| | Illness Perceptions | Control/Cure | + | | | |
| | | Consequences | +,+ | | + | + |
| | | Not specified | + | | | |
| | Medication Beliefs | Necessity | 0,+ | | | |
| | | Concerns | 0,+ | | | |
| | Illness Acceptance | | - | 0 | | |
| Non-RA-related cognitions | Goal Ownership | | | | | + |
| | Role Satisfaction | | - | | - | 0 |
| | Fatigue self-efficacy | | -,- | - | - | - |
| | Fatigue causal attributions | Somatic | - | 0 | | |
| | | Non-somatic | + | 0 | | |
| | Fatigue catastrophizing | Rumination | + | 0 | | |
| | | Helplessness | + | 0 | | |
| | | Magnification | + | - | | |
| | Social Mobilisation self-efficacy | | - | - | | |
| | Neuroticism | | + | 0 | | 0 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | Optimism | | 0,- | 0 | | |
| Personality Traits | Pessimism | | 0 | | | |
| | Self-consciousness | Public | + | + | | |
| | | Private | 0 | 0 | | |
| Stress and Coping | Stress/Hassles | | +,+,+ | | 0 | 0 |
| | Coping | General | 0 | | | |
| | | Worrying | + | + | | |
| | | Praying/Hoping | 0 | | 0 | 0 |
| | | Retreating | + | 0 | | |
| | | Resting | + | 0 | | |
| | | Transformation | + | 0 | | |
| | | Distraction | 0 | | | |
| | | Reducing demands | + | 0 | | |
| Social Support and Interpersonal relationships | Social Support | Perceived quantity | -,- | 0 | 0 | 0 |
| | | Problematic | +,+ | 0,+ | | |
| | | Structural | | 0 | | |
| | | Discrepancies | 0 | | | |
| | | Perceived Adequacy | 0,- | | | |
| | Interpersonal Events | Negative | + | ? | + | ? |
| | | Positive | ? | ? | ? | ? |

+ positive association with fatigue ($p<0.05$); - negative association with fatigue ($p<0.05$); 0 no association with fatigue ($p<0.05$); ? Mixed results

## Affect and Common Mental Disorders

Psychological variables examining aspects of psychological well-being, depression, anxiety, mood or affect were assigned to this group. These variables range from clinically diagnosed depression, to constructs of affect and self-esteem, covering a wide spectrum of mental health states. Twenty-five studies examined associations between mood and common mental disorders and fatigue, nineteen using cross-sectional design, and 6 using prospective design.

The results of the box-analysis of negative affect and common mental disorder are shown in Table 2. At a cross-sectional level, 93.9% (31/33) found significant associations between their affect and common mental disorder variables and fatigue. Increased levels of depression, anxiety and psychological distress, and reduced mental health were all found to

be bivariately associated with increased levels of fatigue. The correlation coefficient values for this association ranged between 0.15 (Barlow et al., 2002; negative affect) and 0.79 (Ibn Yacoub et al., 2012; mental health). One study (Fifield et al., 1998), found mixed results at a bivariate level. The authors report that neither a lifetime diagnosis of major depressive disorder (identified via a diagnostic interview schedule (Robins & Helzer, 1985), nor sub-threshold major depression was significantly associated with current fatigue experience. However, regardless of history of mood disorder, patients experiencing current dysphoria reported significantly higher levels of fatigue than patients not experiencing current dysphoria. This suggests that it is current, rather than previous mood, which is the most reliably associated with experiences of fatigue.

At a multivariate level, most depression and psychological distress retained their significant associations, whereas none of the anxiety, negative affect and self-esteem variables retained a level of statistical significance. Only 37.5% (6/16) results were statistically significant. No clear pattern emerges when considering the covariates included in the multivariate analyses, which could account for the reduction in effect size. Wolfe et al. (1996) found that anxiety and depression were both associated with increased fatigue in bivariate analyses (rs = 0.52 and 0.50 respectively). After including age, sex, body mass index, smoking, sleep disturbance, pain, physical disability, morning stiffness, grip strength, joint count, inflammation, depression, night pain and disease duration (anxiety was omitted due to its collinearity with depression), depression remained a significant predictor of increased fatigue ($\beta$= 0.14, $p<0.001$). Approximately 45% of the variance in fatigue in RA was found to be accounted for by pain, sleep disturbance and depression. By contrast, Riemsma et al. (1998) found that although mood was significantly associated with fatigue in a correlational analysis (0.45, $p<0.001$), a stepwise regression analysis including gender, disease duration, physical function, pain, social support and self-efficacy, resulted in mood being stepped out for the model at an early stage, with no multivariate effect size reported.

Consideration of the longitudinal studies reveal a similar pattern of events. At a bivariate level, 83.3% (5/6) bivariate analyses report significant longitudinal associations between affect and common mental disorder and fatigue outcomes. Only 33.3% (2/6) sustain significant associations after multivariate analysis. Thyberg, Dahlström, & Thyberg (2009) assessed fatigue in early RA patients across three years. Mental health was associated with fatigue consistently across time-points. A principal components analysis was performed for male and female patients separately to identify underlying components in fatigue across three

yearly measurements. For women, mental health was included in a component (also including sleep disturbance, activity limitation and pain) which accounted for 15% of the variance in fatigue at 12 and 24-month follow-ups, and 16% at 36-month follow-up. In men, the component including mental health was only included at 12- and 36-month follow-ups, and accounted for 26% and 17% of the variation in fatigue respectively. In a correlation analysis, Treharne et al. (2008) found that baseline depression was significantly associated with baseline fatigue and fatigue at 1-year follow-up. However in a hierarchical linear regression, depression was added into a model that included several demographic (age, sex, employment status) and clinical (disease duration, medication, inflammation, pain and disability) variables, and the association was rendered non-significant.

The weight of evidence provided here suggests that while negative affect and common mental disorders may have significant implications for fatigue at a bivariate level, this relationship tends to be lost at a multivariate level. There are differences between the variables in this category, with depression and anxiety being more frequently reported than other variables such as mental health, general psychological distress, negative affect and self-esteem. Additionally, there appear to be differential relationships between these variables, with depression and distress more frequently associated with fatigue than negative affect and anxiety.

Examination of the quality summary shown in Table 3 shows that the studies in the affect and common mental disorder category are of mixed quality. Whilst the majority use validated measures of their respective psychological variables (76%), and most reported sufficient eligibility criteria (80%), only 52% used validated, multi-item measures of fatigue. Additionally, only 32% utilised a randomised or consecutive recruitment strategy, and 36% were multi-centre studies and had a reported participation rate of >75%. Only 20% of studies overtly stated that they had sufficient power for their analysis, which may account for why so many affect and common mental disorder variables were no longer significant at a multivariate level.

## RA-related cognitions

Twelve studies examined fatigue in relation to RA cognitions. RA cognitions relate to perceptions or thoughts related to RA, which may be associated with poorer health outcomes. The common sense model of illness (Leventhal, Nerenz, & Steele, 1984) suggests that when faced with a health threat, people create their own perceptions of their illness, which

influence their response to illness. One aspect of illness perceptions includes perceived control over the condition: a lack of perceived control can result in a sense of helplessness (Abramson, Seligman, & Teasdale, 1978). Additionally, RA-cognitions can relate to an individual's self-efficacy, or their assessment of whether they have the resources to be able to manage prospective situations (Bandura, 1977).

The results of the box-analysis of RA-related cognitions are shown in Table 2. At a cross-sectional bivariate level, 88.9% (16/18) analyses yielded significant associations. Increased levels of fatigue were associated with reduced general self-efficacy (r=-0.30, r=-0.44) as well as reduced efficacy over pain (r=-0.54), other symptoms (r=-0.30; r=-0.52), function (r=-0.45) and RA coping (r=-0.47), increased levels of helplessness (rs= -0.32-0.49), perceptions of the disease being uncontrollable/incurable (r=-0.20), as having significant consequences (r=0.33), and reduced illness acceptance (r=-0.49). Rezvani et al., (2012) found an association between illness perceptions and fatigue (r= 0.55, $p<0.001$), however did not clarify which specific illness perceptions were associated with fatigue. Mixed evidence was found for the perceptions of medication beliefs and concerns about medication. Treharne et al. (2005) examined fatigue in relation to beliefs about RA medication and found no significant association between perceptions of medication necessity nor medication concerns and fatigue (rs = 0.12 and 0.16 respectively). These findings are at odds with Neame & Hammond (2005) who found that concerns about medication (r=0.29, $p<0.001$) and beliefs about medication necessity(r=0.30, $p<0.001$) were significantly associated with increased fatigue.

At a multivariate level, relationships between general self-efficacy and coping self-efficacy were sustained after adjusting for several covariates. Cross et al. (2008) created regression models including the variables: comorbidities, physical and mental aspect of QoL, pain, stiffness, function, disability, and mental health. Reduced levels of self-efficacy for other symptoms remained a significant predictor of increased fatigue when measured by the Fatigue Severity Scale (FSS; Neuberger, 2003) ($\beta$=-0.44, $p<0.01$). The entire model (including vitality and other symptom self-efficacy) accounted for 48% of the variance in FSS fatigue severity. Riemsma et al. (1998) performed a stepwise multiple regression analysis including gender, disease duration, health status, physical function, pain, affect, social support and social mobilisation found that RA self-efficacy remained a significant predictor of increased fatigue, accounting for 33% of the variance in fatigue (B=-4.89, $p<0.01$).

Very few RA-related cognitions were measured longitudinally, however where they were, they were universally found to be associated with fatigue in both bivariate and multivariate analyses. Treharne et al. (2008) used the Illness Perception Questionnaire (IPQ; Weinman, Petrie, Moss-Morris, & Horne, 1996) to measure patients' perceptions of RA consequences, and the Arthritis Self-Efficacy Scale (ASES; Lorig, Chastain, Ung, Shoor, & Holman, 1989) to measure perceived self-efficacy over other symptoms of RA, such as fatigue and mood. Both increased perceptions of consequences and reduced self-efficacy were found to be significantly correlated with higher levels of fatigue both at baseline (0.32, -0.42, ps<0.001 respectively) and at 1-year follow-up (0.40, -0.36, ps<0.001 respectively). Five hierarchical linear regression models were created, including an increasing number of variables. Perceptions of consequences and self-efficacy were entered in the final two models, and in the final model, also including age, gender, employment status, disease duration, medication, inflammation, pain, disability impact, sleep disruption, depressed mood, and coping, both perceptions of consequences ($\beta$= 0.30, p<0.05) and self-efficacy ($\beta$= -0.27, p=0.06) at baseline remained significant predictors of fatigue at 1-year follow-up, showing the largest coefficient sizes in the model. Baseline perceptions of illness consequences and self-efficacy explained 9% of the variance in fatigue at 1-year follow-up.

Examination of the quality synthesis in Table 3 shows the mixed level of quality seen in the studies examining RA-related cognitions. A total of 91.7% used validated measures of psychological variables, however only 50% used validated measurements of fatigue and reported eligibility criteria. Only 33.3% of studies used randomised/consecutive recruitment strategies, and the same number recruited patients from multiple centres. Only 16.7% reported a participation rate of >75% and specifically stated that they had sufficient power for their analysis.

## Non-RA-related cognitions

Four studies examined a range of non-RA-related cognitions, such as goal ownership, role satisfaction, and self-efficacy not related specifically to RA. Distorted or maladaptive perceptions may inhibit effective management of fatigue, and thus contribute to the perpetuation of fatigue symptoms (Tack, 1990).

The results of the box-analysis of non-RA-related cognitions are shown in Table 2. The cross-sectional bivariate analyses show that in 100% of results, a significant association was found. Increased levels of fatigue were associated with reduced role satisfaction (r=-0.40),

reduced fatigue self-efficacy (r=-0.46), reduced somatic fatigue causal attributions (r=-0.26), increased non-somatic fatigue causal attributions (r=0.14), increased fatigue catastrophizing rumination (r=0.31), helplessness (r=0.39) and magnification (r=0.21).

After adjusting for covariates in multivariate analyses, significant associations were found between fatigue self-efficacy, fatigue magnification catastrophizing, and social mobilisation self-efficacy and fatigue. Riemsma et al. (1998) assessed 229 outpatients' perceptions of social mobilisation; their expectations regarding capability to obtain help from their social network if needed. A stepwise multiple regression analysis including gender, disease duration, physical function, pain, affect, social support and RA coping self-efficacy found that reduced social mobilisation self-efficacy remained a significant predictor of increased fatigue (B=-4.54, β=-0.17, $p<0.01$), predicting approximately 36% of the variance in fatigue.

Van Hoogmoed et al. (2010) used the SES-28 to measure fatigue self-efficacy and found it to be significantly associated with fatigue both at bivariate level, and also after a chunk-wise backward regression analysis (β=-0.20, $p<0.001$). Additionally, the magnification element of fatigue catastrophizing remained a significant predictor of fatigue in the final model (β=-0.11, $p<0.05$). The final model (including age, Rheumatoid Factor status, pain, physical function, depressive thoughts, fatigue self-efficacy, worrying, magnification of fatigue and sleep disturbances) accounted for 63% of the variance in fatigue.

In the longitudinal studies at a bivariate level, increased fatigue at follow-up was found to be associated with reduced role satisfaction and fatigue self-efficacy at baseline. At a multivariate level, reduced goal ownership and fatigue self-efficacy at baseline were associated with increased fatigue at follow-up, although role satisfaction lost its association with fatigue. Maes et al. (2006) used the Treatment Self-Regulation Questionnaire (TSRQ; Levesque et al., 2007) to assess goal ownership, and found that it significantly predicted fatigue at one-year follow-up, after controlling for socio-demographic and disease variables in a hierarchical regression analysis. Strengthening perceptions of goal ownership may help to reduce fatigue in RA. Mancuso et al. (2006) examined perceptions of role satisfaction and found that reduced role satisfaction at baseline was correlated with increased fatigue at one-year follow-up (r=0.37, $p<0.001$). However in a multivariate model including gender, age, comorbidities, mood, disability, social support, pain, sleep quality, physical activity and disease variables, perceived role satisfaction was no longer associated with fatigue at follow-up.

Assessment of study quality reveals fairly poor study quality in the small number of papers examining non-RA-related cognitions. A total of 66.7% used validated measures for psychological variables ad fatigue, and stated eligibility criteria. None of the studies used randomised/consecutive recruitment strategies, multi-centre recruitment, stated a participation rate of >75% or stipulated that they were adequately powered for their analysis.

## Personality Traits

Several models of fatigue suggest that certain personality traits, notably perfectionist tendencies and neuroticism (Surawy, Hackmann, Hawton, & Sharpe, 1995), may pre-dispose individuals to develop fatigue disorders, and that traits such as extraversion may be protective against fatigue (Michielsen, De Vries, & Van Heck, 2003). Four studies examined the role of three personality traits on fatigue: neuroticism, optimism and self-consciousness.

The results of the box-analysis of personality traits are shown in Table 2. Only 50% of bivariate analyses revealed fatigue to be significantly associated with personality traits. Increased levels of fatigue were found to be associated with increased neuroticism (r=0.44), and increased public self-consciousness (r=0.22). Mixed evidence was found for the relationships between optimism and fatigue.

At a multivariate level, only public self-consciousness was found to be associated with fatigue. Treharne et al. (2005) performed a multivariate analyses taking into account demographics, psychosocial variables and disease duration were created to examine the main effects of these variables on fatigue. Fatigue was found to be lower in patients with low public self-consciousness (M= 41.5, SD= 24.2) than in those with high public self-consciousness (M=53.9, SD= 22.9; $F(1,76) = 7.1$, $p<0.01$).

Only neuroticism was examined with any element of follow-up. Stone et al. (1997) examined neuroticism in relation to fatigue in Ecological Momentary Assessment, looking at diurnal cycles and within-day fatigue variation, however it was not found to be significantly associated with variability of fatigue throughout the day.

Quality assessment, shown in Table 3, shows that in general, study quality in this group was higher than in other categories. 100% of studies used validated assessments of personality, and 75% used validated fatigue assessments. 75% reported eligibility criteria, and 50% recruited from multiple site. 25% reported a participation rate >75%, however no studies used

randomised/consecutive recruitment strategies, or stated if they were sufficiently powered for their analysis.

## Stress and Coping

Increased stress is thought to be associated with increased levels of fatigue in RA, through the increased stimulation of interleukin-6 caused by stress, which in turn, is associated with increased levels of fatigue (Davis et al., 2008). Not only the increase in perceived stress, but also the coping mechanisms used to manage stress may therefore be crucially associated with fatigue in RA. Five studies examined the relationships between stress and coping and fatigue.

At a cross-sectional, bivariate level (Table2), 77.8% of studies reported a significant association between stress and coping variables and fatigue. Increased fatigue was associated with increased levels of stress/hassles (rs= 0.43, 0.37, 0.39), increased worrying coping (r=0.49), retreating coping (r=0.22), resting coping (r=0.19), and fatigue transformation coping (r=0.23), reducing demands (r=0.22). No significant bivariate associations were found between general coping strategies and fatigue, nor praying/hoping coping or distraction coping and fatigue. In multivariate analysis, only worrying coping retained its significant association with fatigue ($\beta$=-0.21, $p<0.05$; van Hoogmoed et al., 2010).

In longitudinal analyses, no stress/coping variables were found to be associated with fatigue either at bivariate or multivariate level. Treharne et al. (2008) examined praying/hoping coping strategies in 114 patients with RA. In a correlation analysis, baseline coping was not significantly associated with fatigue at either baseline (r=0.19, $p>0.05$) or at 1-year follow-up (r=0.04, $p>0.05$). When included in a hierarchical linear regression model, also including several demographic, psychological and disease variables, coping was not predictive of fatigue at one-year follow-up ($\beta$=-0.04, $p>0.05$).

Assessment of study quality (table 3) shows that 100% and 60% of these studies used validated measures of stress/coping variables and fatigue respectively. Only 20% used randomised or consecutive recruiting strategies, and 40% recruited from multiple sites. All of the studies (100%) reported eligibility criteria, however a vast minority (20%) had adequate levels of participation or stated that they were well-powered for their analysis.

## Social Support and Interpersonal Relationships

The extent to which an individual feels that they have sufficient support and assistance available if required may be a crucial aspect in the management of fatigue in RA; it can assist in the self-management of the condition, adherence to medication and recommended lifestyle changes (Taal, Rasker, Seydel, & Wiegman, 1993). However social support is not always positive. Problematic, unwanted or stressful interpersonal relationships may result in increased stress, depression and fatigue in RA (Revenson, Schiaffino, Majerovitz, & Gibofsky, 1991). Therefore it is not only the quantity of social support which is important, but also the quality of that social support. Seven studies examined the relationship between social support and fatigue.

At a cross-section bivariate level (table 2), 66.7% of analyses found significant assocaitions between social support and fatigue. Increased fatigue was found to be associated with reduced perceived quantity of social support (rs=-0.26 and -0.24 ) and increased problematic social support (rs=0.14 and 0.28). Mixed evidence was found for perceived adequacy of social support.

In the multivariate analyses, only two analyses continued to find social support (problematic) to be associated with fatigue. Riemsma et al. (1998) measured both social support and problematic social support in 229 RA outpatients. Increased problematic social support remained a significant predictor of fatigue when included in a multiple regression analysis including gender, disease duration, physical function, pain, affect and self-efficacy (B= 4.64, $\beta$=0.13, $p<0.05$), accounting for 37% of the variance in fatigue in total.

Mixed evidence was found for positive and negative interpersonal events, both in same-day and next-day assessments of fatigue. Davis, Okun, Kruszewski, Zautra, & Tennen (2010) examined the relationship between daily interpersonal events and same- and next-day fatigue. They report that a higher than average number of negative interpersonal events was associated with increased levels of same-day fatigue. Changes in positive interpersonal events were associated with reduced fatigue in women, but not men. However this interaction became non-significant after controlling for affect. The relationship between the interaction between positive interpersonal events and female gender and same day fatigue was found to be mediated by positive affect. Similarly, changes in negative interpersonal events and same-day fatigue was found to be mediated by negative affect. Same-day fatigue and number of negative interpersonal events were strong predictors of next-day fatigue. There was a

significant interaction between gender and interpersonal events, whereby days with increased positive interpersonal experiences were associated with higher levels of next-day fatigue for women but not men. Negative affect was also found to partially mediate the pathway between negative interpersonal events and next-day fatigue.

No other significant associations were found in longitudinal assessments of fatigue and social support. Mancuso et al. (2006) used the Duke Social Support and Stress Scale (Parkerson, Broadhead, & Tse, 1991) to examine perceived social support and stress and their associations with long-term fatigue. After controlling for other psychosocial and disease variables. At one-year follow-up, neither baseline social stress (r=0.19, p=0.07) nor social support (r=0.16, p=0.13) were associated with fatigue in bivariate or multivariate analysis.

The association between social support and fatigue is varied. There is some evidence to suggest that negative or problematic social support is associated with poorer fatigue outcomes, and that positive social support is associated with reduced fatigue. However the limited number of studies prevents solid conclusions being formed. Assessment of study quality shows that 100% of studies used a validated measure of social support, and 57.1% a validated measure of fatigue. Only 14.3% used randomised/consecutive reporting strategies, and 42.9% recruited from multiple centres. In total, 85.7% stated their eligibility criteria, and 14.3% reported a participation rate of >75%. No studies stated whether they were adequately powered for their analysis.

# Discussion

## *Summary of findings*

The aim of this review was to identify studies of psychological variables and their associations with fatigue in RA. A systematic search of the literature revealed several psychological correlates of fatigue which were grouped into six categories: affect and common mental disorders, RA-related cognitions, non-RA related cognitions, personality traits, stress and coping, and social support and interpersonal relationships.

There was some evidence to support the link between mood and fatigue, with many studies finding an association between low mood and higher levels of fatigue. However at a multivariate level, several studies show non-significant associations. Whilst mood may be related to fatigue, its collinearity with other variables such as increased pain perception

**Table 3. Quality assessment for combined analysis of specific variables**

| Category | Validated measure of psychological variable? | Multi-item measure of fatigue? | Randomised /consecutive recruitment strategy? | Multi-centre? | Eligibility criteria specified? | Participation rate >75% | Adequately powered? |
|---|---|---|---|---|---|---|---|
| | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Affect and common mental disorder (N=25) | 76.0% | 52.0% | 32.0% | 36.0% | 80.0% | 36.0% | 20.0% |
| RA-related cognitions (N=12) | 91.7% | 50.0% | 33.3% | 33.3% | 50.0% | 16.7% | 16.7% |
| Non-RA-related cognitions (N=3) | 66.7% | 66.7% | 0.0% | 0.0% | 66.7% | 0.0% | 0.0% |
| Personality Traits (N=4) | 100.0% | 75.0% | 0.0% | 50.0% | 75.0% | 25.0% | 0.0% |
| Stress and Coping (N=5) | 100.0% | 60.0% | 20.0% | 40.0% | 100.0% | 20.0% | 20.0% |
| Social Support and Interpersonal relationships (N=7) | 100.0% | 57.1% | 14.3% | 42.9% | 85.7% | 14.3% | 0.0% |
| Total | 79.3% | 48.3% | 31.0% | 37.9% | 72.4% | 31.0% | 30.7% |

(Dickens, McGowan, & Dale, 2003), inflammation (Howren, Lamkin, & Suls, 2009) and other socioeconomic variables (Lorant et al., 2003) may dilute its influence on multivariate analyses. Similarly, there was relatively consistent evidence that RA-related cognitions were related to fatigue, for example, reduced self-efficacy was associated with increased fatigue. Although limited in number, longitudinal studies reveal a potentially persistent association between RA cognitions (self-efficacy for other symptoms and perceptions of illness consequences) and fatigue over time. Moreover, several studies suggested that non-RA related cognitions (such as fatigue self-efficacy and goal ownership) were associated with fatigue, although again, these relationships were often not sustained at a multivariate level. The review found no conclusive evidence for an association between personality traits and fatigue. Fairly consistent bivariate associations were found between stress/coping and fatigue, however these were not supported in multivariate analyses and longitudinal designs. Inconsistent evidence was found relating social support and fatigue, highlighting the complex nature of social support in relation to health: there are elements of reverse causality whereby the existence of fatigue may in itself alter both perceptions and availability of social support; personality factors such as neuroticism or hostility may confound relationships between social support and health; and there are pertinent cultural and personal differences in perceptions of "adequate" social support quality and quantity (Thoits, 2011).

Importantly, the results of our study suggest that disease-related factors such as disease activity, pain, physical function, medication and stiffness play an important role in fatigue levels. In some of the included studies, we found that psychological variables (such as anxiety, depression, helplessness, life stress, and coping) were no longer significantly associated with fatigue after controlling for disease related factors. Disease activity appears to play a role in the relationship between psychological variables and fatigue, however further research and similar systematic review methodology is needed in order to identify whether disease activity acts as a mediator.

Similarly, self-efficacy also appears to be an important factor in the relationship between fatigue and mood. In two of the included studies, the association between fatigue and mood became non-significant after controlling for self-efficacy (Riemsma et al., 1998). However, as neither of the studies were prospective, it was not possible to ascertain whether self-efficacy acted as a mediator.

## *A cognitive behavioural model of fatigue in RA*

Hewlett et al's (2011b) model of fatigue in RA suggested that there is an interaction between RA-related factors, cognitive-behavioural factors, and personal factors, which interact to maintain fatigue. This review sought to systematically review and synthesise the evidence base for the psychological components of fatigue, and consequently we propose a psychological model of fatigue in RA (Figure 3). This is consistent with cognitive-behavioural models of fatigue in other illnesses such as chronic fatigue syndrome (Surawy et al., 1995; Chalder, Butler, & Wessely, 1996) and cancer (Armes, Chalder, Addington-Hall, & Hotopf, 2007). The onset of fatigue may be associated with a trigger (such as inflammation), and fatigue then develops and is maintained over time by disease activity but also factors such as low affect, unhelpful cognitions, avoidant coping and lack of social support, which interact with each other. People may find themselves in a vicious circle in which they do not have the self-efficacy to break. For example, a perception of RA as being uncontrollable or having serious consequences may lead an individual to reduce their activities in an attempt to control the symptoms but which has the unfortunate consequence of making the fatigue worse. Similarly, cognitions that are not specific to RA, such as fatigue self-efficacy, fatigue catastrophising and role satisfaction, may contribute to fatigue. In addition, unwelcome or unwanted social input may increase fatigue levels. Conversely, high levels of RA-self-efficacy, illness acceptance and positive social support may help an individual to manage fatigue levels more effectively.

Rigorous and systematic assessment of the disease-related and environmental variables suggested by Hewlett et al. (2011b) would further contribute to strengthening a holistic model of fatigue in RA.

## *Strengths and limitations*

A strength of this review is that it was conducted using a rigorous and replicable methodology, with abstract screening and data extraction being carried out by independent researchers in order to reduce bias.

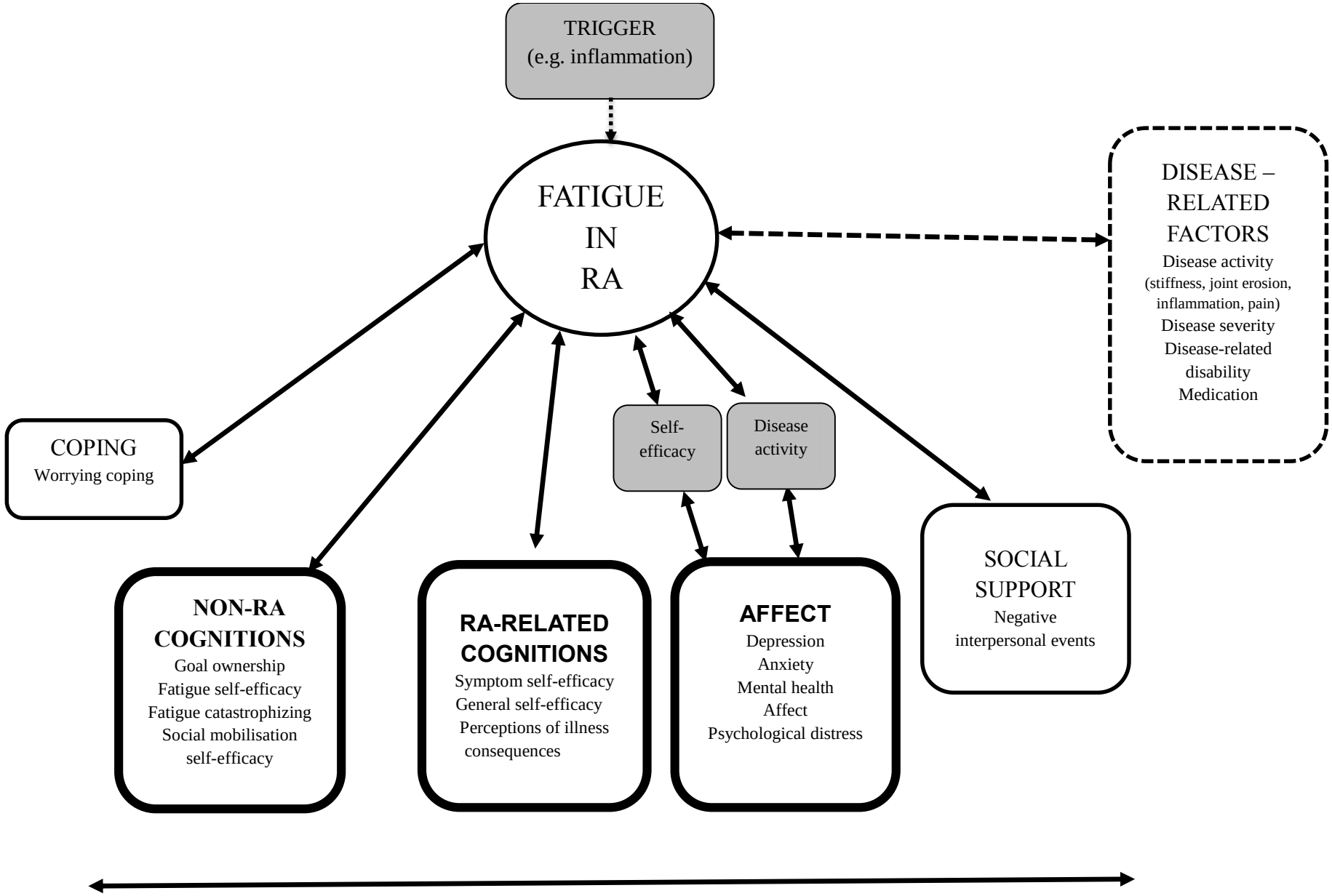
However this review also has some limitations. It is possible that it could have been influenced by publication bias. As the broad scope of this review, and vast heterogeneity both between and within psychological categories precluded a meta-analysis, it was not possible to formally assess the extent of publication bias using a funnel plot or sensitivity analysis. In

future reviews, it may be beneficial to include 'grey literature', as this is more likely to report negative findings and therefore give a more balanced view of the literature. The quality of the included studies was varied. Both cross-sectional and prospective studies were included, although the majority of studies were cross-sectional. Therefore there was a limit to the conclusions that could be drawn about cause and effect. The measures used in this study were heterogeneous and varied between visual analogue scales and multi-item psychometric scales. The majority of measures however had been validated. Many of the disease-related factors examined in this review (such as pain, physical activity, and disease severity) were self-reported. It is likely that objective measurements give a more robust representation of disease activity than self-report measures. Mood may act as a confounder for self-reported measures of disease activity (Ward, 1994), and self-reported disease activity could potentially be over-reported in patients who are experiencing depression or fatigue.

Although most studies used an appropriate statistical method for analysing the data many studies did not account for the presence of confounding variables during the analysis. Many studies did not provide a sample size calculation or power analysis in order to justify the size of their sample. Also, very few studies reported data on retention rates and the completeness of follow up. The majority of studies described detailed demographic sample characteristics such as gender, age and disease duration, although many did not specify details such as ethnicity or socio-economic status. Therefore it is difficult to assess the representativeness of these samples. Only around two thirds of the included studies reported a recruitment strategy. Of these, the majority used consecutive sampling and convenience sampling from outpatient clinics. An advantage of this kind of sampling is that it is less vulnerable to selection bias because the participants are likely to be less selected than in randomised controlled trials. However, very few of the included studies described their inclusion and exclusion criteria. Therefore it was not possible to assess for the presence of selection bias.

A further consideration is the measurement of such complex psychological variables. Personality is a complex and challenging construct, often measured according to the "Big Five" traits: extraversion, agreeableness, conscientiousness, neuroticism, and openness to experience (Goldberg, 1990). However a focus on the Big Five may result in the omission of several other traits which may influence health and well-being. Cloninger and Zohar (2012) for example, report that self-directedness, cooperativeness and self-transcendence are all associated with well-being. The results of the current review also suggest that self-consciousness may be an important construct. Establishing the impact of personality on

**Figure 3. A conceptual model of fatigue in rheumatoid arthritis based on research evidence**






Footnote: Bidirectional arrows represent evidence-based associations between variables as found in this review. Factors with a greater weight of evidence are shown in bold. Dotted boxes indicate fields where further systematic review evidence is needed. Hypothesised variables are indicated using shaded boxes.

health outcomes is challenging to determine due to the interrelatedness between personality traits. Single-trait questionnaires such as the Life Orientation Test may be insufficient to capture the complexity of personality, and make it challenging to determine whether a personality trait is independent, works interactively with other traits to impact health, or is redundant (Korotkov & Hannah, 2004). Our conclusions relating to personality and fatigue are therefore limited by a small quantity of studies, focused on independent traits, rather than the broader spectrum of personality.

## *Clinical implications*

The findings of this review have many clinical implications. For example, although fatigue is commonly reported in RA patients, it is not consistently measured as an outcome in clinical studies of RA (Kalyoncu et al., 2009). It has been suggested that all studies of RA should include fatigue as a routine outcome variable, because of its significance to patients and its responsiveness to treatment (Kirwan et al., 2007). Fatigue can be assessed when patients first present to primary and secondary care, and continually monitored throughout the course of treatment. Early identification and management may prevent acute fatigue from becoming chronic.

The results of this review suggest that fatigue is correlated with several psychological factors which are amenable to change (Cramp et al., 2013). Motivational interviewing could be used to foster motivation and encourage people with RA to change health behaviours, such as physical activity (Bode et al., 2008; Hurkmans et al., 2010). Healthcare staff at rheumatology clinics could be trained to deliver minimal interventions based on cognitive behavioural approaches, therefore helping patients to self-manage the disease (Dures & Hewlett, 2012). Brief interventions may provide a preferable, more accessible and cost-effective solution to the treatment of fatigue compared to traditional Cognitive Behavioural Therapy (CBT).

Our model highlights the importance of mood and affect on fatigue levels in RA and research suggests that depression is highly prevalent in RA patients (Matcham, Rayner, Steer & Hotopf, 2013). Psychological or pharmacological treatment of emotional symptoms may have a beneficial effect on fatigue levels. More specifically, non-pharmacological interventions such as cognitive behavioural therapy, relaxation and stress-management may be useful additions to traditional medical treatments for mood disorders in RA (Cramp et al., 2013).

Cognitive-behavioural approaches to managing rheumatic diseases often include recognising links between cognitions, behaviours and symptoms and using strategies such as self-monitoring, cognitive restructuring, relaxation, and goal setting to help patients self-manage their illness (Dures & Hewlett, 2012). There is some evidence that CBT for RA can lead to positive outcomes such as improved coping, well-being and self-efficacy, as well as reduced fatigue and depression (Sharpe, Sensky, Timberlake, Ryan, Brewin & Allard, 2001; Evers, Kraaimaat, van Riel & de Jong, 2002; Hammond, Bryan, & Hardy, 2008; Hewlett et al., 2011a).

RA interventions that are not targeted specifically towards fatigue but focus on ameliorating disease related factors directly, can lead to a reduction in fatigue (Hewlett et al., 2011a). Indeed, our review showed that disease-related factors were associated with fatigue, and therefore targeting specific disease related factors may help to reduce symptoms of fatigue. For example, disease-modifying drugs and anti-TNF drugs have been shown to reduce fatigue in people with RA (Pollard et al., 2006).

### *Recommendations for future research*

Based on the quality assessment of the studies included in this review, we can offer some recommendations for future studies of psychological correlates of fatigue in RA.

Firstly, studies should have a prospective design so that causal associations and mediators can be examined (for example, using multiple regression analysis). The sample size should be large enough for a well-powered statistical analysis, and to account for attrition during the course of the study.

In order to reduce selection bias, participants should be recruited consecutively from primary or secondary care, and reasons for exclusion should be clearly stated. Ideally, patients would all be at the same stage of disease so that disease duration can be controlled for. The study should also take into account any treatment the patient has had.

A model of understanding fatigue in the context of RA should be based on previous theory and evidence taking account of biological, psychological and social factors. When conducting new research the choice of measures should then be guided by the model. In addition, disease activity should be assessed using both objective and subjective measures and controlled for when measuring the association between psycho-social variables and fatigue.

Future studies could investigate the effectiveness of targeted interventions for fatigue in RA. A randomised controlled trial design could be used in order to investigate the effectiveness of CBT as compared to treatment as usual. Several measures of fatigue could be used in order to capture the multidimensionality of fatigue. Additionally, psychological variables such as, unhelpful thoughts and avoidance behaviour which may play a role in the maintenance of fatigue could be examined as possible mediators.

## *Conclusions*

This review has shown that fatigue in RA is associated with a number of psychological, social and disease-related factors. These relationships have been illustrated in the form of a cognitive-behavioural model of fatigue in RA. Longitudinal studies are needed in order to understand the nature of fatigue in RA and any causal relationships with psycho-social factors. Individuals with RA fatigue may benefit from pharmacological and psychological interventions which target these factors.

## References


Abramson, L. Y., Seligman, M. E., & Teasdale J. D. (1978). Learned helplessness in humans: Critique and reformulation. *Journal of Abnormal Psychology*, 87, 49-74.

Alamanos, Y., Vougari, P. V., & Drosos A. A. (2006). Incidence and prevalence of rheuamtoid arthritis, based on the 1987 American College of Rheumatology criteria: A systematic review. *Seminars in Arthritis and Rheumatism*, 36, 182-188.

Armes, J., Chalder, T., Addington-Hall, J., & Hotopf, M. (2007). A randomized controlled trial to evaluate the effectiveness of a brief, behaviorally oriented intervention for cancer-related fatigue. *Cancer,* 110, 1385-95.

Bandura, A. (1977). Self-efficacy: toward a unifying theory of behavioral change. *Psychological review*, 84, 191-215.

*Barlow, J. H., Cullen, L. A. & Rowe, I. F. (2002). Educational preferences, psychological well-being and self-efficacy among people with rheumatoid arthritis. *Patient Education and Counseling,* 46, 11-19.

*Belza, B. L., Henke, C. J., Yelin, E. H., Epstein, W. V., & Gilliss, C. L. (1993). Correlates of fatigue in older adults with rheumatoid arthritis. *Nursing Research*, 42, 93-99.

*Belza, B. L. (1995). Comparison of self-reported fatigue in RA and controls. *The Journal of Rheumatology*, 22, 639-643.

Bode, C., Taal, E., Emons, P. A., Galetzka, M., Rasker J., and Van de Laar, M. F. J. (2008). Limited results of group self-management education for rheumatoid arthritis patients and their partners: explanations from the patient perspective. *Clinical Rheumatology* 27, 1523-1528.

*Brekke, M., Hjortdahl, P., & Kvien, T. K. (2003). Changes in self-efficacy and health status over 5 years: A longitudinal observational study of 306 patients with rheumatoid arthritis. *Arthritis Care & Research*, 49, 342-348.

Chalder, T., Butler, S., and Wessely, S. (1996). In-patient treatment of chronic fatigue syndrome. *Behavioural and Cognitive Psychotherapy*, 24, 351-365.

Chauffier, K., Salliot, C., Berenbaum, F., & Sellam, J. (2012). Effect of biotherapies on fatigue in rheumatoid arthritis: A systematic review of the literature and meta-analysis. *Rheumatology*, 51, 60-68.

Cloninger, C. R. & Zohar, A. H. (2013). Personality and the perception of health and happiness. *Journal of Affective Disorders*, 128, 24-32.

*Covic, T., Tyson, G., Spencer, D., Howe, G. (2006). Depression in rheumatoid arthritis patients: Demographic, clinical, and psychological predictors. *Journal of Psychosomatic Research*, 60, 469-476.

Cramp, F., Hewlett,S, Almeida, C., Kirwan J. R., Choy E. H. S., Chalder, T., Pollock J., & Christensen, R. (2013) Non-pharmacological interventions for fatigue in rheumatoid arthritis. Cochrane Database of Systematic Reviews DOI: 10.1002/14651858.CD008322.pub2.

*Cross, M., Lapsley, H., Barcenilla, A., Brooks, P., & March, L. (2008). Association between measures of fatigue and health-related quality of life in rheumatoid arthritis and osteoarthritis. *The Patient: Patient-Centered Outcomes Research,* 1, 97-104.

*Davis, M. C., Okun, M. A. Kruszewski, D., Zautra, A. J., & Tennen, H. (2010). Sex differences in the relations of positive and negative daily events and fatigue in adults with rheumatoid arthritis. *The journal of pain : official journal of the American Pain Society* 11, 1338-1347.

Davis, M. C., Zautra, A. J., Younger, J., Motivala, S. J., Attrep, J., and Irwin, M. R. (2008). Chronic stress and regulation of cellular markers of inflammation in rheumatoid arthritis: Implications for fatigue. *Brain, Behavior, and Immunity,* 22, 24-32.

Dickens, C., McGowan, L., and Dale, S. (2003). Impact of depression on experimental pain perception: A systematic review of the literature with meta-analysis. *Psychosomatic Medicine,* 65, 369-375.

Druce, K. L, Jones, G. T., Macfarlane, G. J., & Basu, N. (2014). Patients receiving anti-TNF therapies experience clinically important improvements in RA-related fatigue: Results from the British Society of Rheuamtology Biologics Register for Rheuamtoid Arthritits. *Rheumatology*, doi: 10.1093/rheumatology/keu390.

Dures, E. and Hewlett, S. (2012). Cognitive-behavioural approaches to self-management in rheumatic disease. *Nature Reviews Rheumatology*, 8, 553-559.

Evers, A. W. M., Kraaimaat, F. W., van Riel, P. L. C. M., & de Jong, A. J. L. (2002). Tailored cognitive-behavioral therapy in early rheumatoid arthritis for patients at risk: a randomized controlled trial. *Pain* 100, 141-153.

*Fifield, J., Tennen, H., Reisine, S., & McQuillan, J. (1998). Depression an dthe long-term risk of pain, fatigue and disability in patients with rheumatoid arthritis. *Arthritis & Rheumatism*, 41, 1851-1857.

Goldberg, L. R. (1990). An alternative "description of personality": The Big-Five factor structure. *Journal of Personality and Social Psychology*, 59, 1216-1229.

Green, B. F. & Hall, J. A. (1984). Quantitative methods for literature reviews. *Annual Review of Psychology, 35*, 37-53.

Hammond, A., Bryan, J., & Hardy, A. (2008). Effects of a modular behavioural arthritis education programme: a pragmatic parallel-group randomized controlled trial. *Rheumatology*, 47, 1712-1718.

Hewlett, S., Cockshott Z., Byron M., Kitchen K., Tipler S., Pope D., & Hehir, M. (2005). Patients' perceptions of fatigue in rheumatoid arthritis: Overwhelming, uncontrollable, ignored. *Arthritis Care & Research*, 53, 697-702.

Hewlett, S., Ambler, N., Almeida, C., Cliss, A., Hammond, A., Kitchen, K., Knops, B., Pope, D., Spears, M., Swinkels, A., & Pollock, J. (2011a). Self-management of fatigue in rheumatoid arthritis: a randomised controlled trial of group cognitive-behavioural therapy. *Annals of the Rheumatic Diseases*, 70, 1060-1067.

Hewlett, S. (2011b). Fatigue in rheumatoid arthritis: Time for a conceptual model. *Rheumatology*, 50, 1004-1006.

Howren, M. B., Lamkin, D. M., & Suls, J. (2009). Associations of depression with c-reactive protein, IL-1, and IL-6: A meta-analysis. *Psychosomatic Medicine*, 71, 171-186.

Hurkmans, E. J., Maes, S., de Gucht, V., Knittle, K., Peeters, A. J., Ronday, H. K., & Vlieland, T. P. M. V. (2010). Motivation as a determinant of physical activity in patients with rheumatoid arthritis. *Arthritis Care & Research*, 62, 371-377.

*Huyser, B. A., Parker, J. C., Thoreson, R., Smarr, K. L., Johnson J. C., & Hoffman, R. (1998). Predictors of subjective fatigue among individuals with rheumatoid arthritis. *Arthritis and Rheumatism*, 41, 2230-2237.

*Ibn Yacoub, Y., Amine, B., Laatiris, A., Wafki, F., Znat, F., & Hajjaj-Hassouni. (2012). Fatigue and severity of rheumatoid arthritis in Moroccan patients. *Rheumatology International*, 32, 1901-7.

*Jump, R. L., Fifield, J., Tennen, H., Reisine, S. & Giuliano, A. J. (2004). History of affective disorder and the experience of fatigue in rheumatoid arthritis. *Arthritis Care & Research*, 51, 239-245.

Kalyoncu, U., Dougados, M. , Daurès, J.-P. & Gossec, L. (2009). Reporting of patient-reported outcomes in recent trials in rheumatoid arthritis: A systematic literature review. *Annals of the Rheumatic Diseases*, 68, 183-190.

Kirwan, J. R., Minnock, P., Adebajo, A., Bresnihan, B. B, Choy, E., de Wit, M., Hazes, M., Richards, P., Saag, K., Suarez-Almazor, M., Wells G., & Hewlett S. (2007). Patient perspective: fatigue as a recommended patient centered outcome measure in rheumatoid arthritis. *The Journal of Rheumatology*, 34, 1174-1177.

Korotkov, D., & Hannah, T. E. (2004). The five-factor model of personality: Strengths and limitations in predicting health status, sick-role and illness behaviour. *Personality and Individual Differences*, 36, 187-199.

Kvien, T. K. (2004). Epidemiology and burden of illness in rheumatoid arthritis. *Pharmacoeconomics*, 22, 1-12.

Leventhal, H., Nerenz, D. R., & Steele, D. J. (1984). Illness representations and coping with health threats. A Handbook of Psychology and Health. A. S. Baum, J. Jillsdale (NJ), Erlbaum: 219-252.

Levesque, C. S., Williams, G. C., Elliot, D., Pickering, M. A., Bodenhamer B., & Finley, P. J. (2007). Validating the theoretical structure of the Treatment Self-Regulation Questionnaire (TSRQ) across three different health behaviors. *Health Education Research*, 22, 691-702.

Loge, J. H., Ekeberg, O., & Kaasa, S. (1998). fatigue in the general Norwegian population: Normative data and associations. *Journal of Psychosomatic Research*, 45, 53-65.

Lorant, V., Deliège, D., Eaton, W., Robert, A., Philippot, P. & Ansseau, M. (2003). Socioeconomic inequalities in depression: A meta-analysis. *American Journal of Epidemiology*, 157, 98-112.

Lorig, K., Chastain, R. L., Ung, E., Shoor, S., & Holman, H. R. (1989). Development and evaluation of a scale to measure perceived self-efficacy in people with arthritis. *Arthritis & Rheumatism*, 32, 37-44.

Luqmani, R., Hennell, S., Estrach, C., Birrell, F., Bosworth, A., Davenport, G., et al. British society for rheumatology and British health professionals in rheumatology guideline for the management of rheumatoid arthritis (the first 2 years). *Rheumatology*, 45, 1167-9.

*Maes, S, K. P., de Gucht, V., Ruehlman, L.S., Heiser, W. (2006). The self regulation skills battery (SRSB). Leiden/Phoenix (AZ), Leiden University/Arizona State University.

*Mancuso, C. A., Rincon, M., Sayles, W. & Paget, S. A. (2006). Psychosocial variables and fatigue: A longitudinal study comparing individuals with rheumatoid arthritis and healthy controls. *The Journal of Rheumatology*, 33, 1496-1502.

Matcham, F., Rayner, L., Steer, S., & Hotopf, M. (2013). The prevalence of depression in rheumatoid arthritis: A systematic review and meta-analysis. *Rheumatology*, 52, 2136-2148.

Matcham, F., Scott, I. C., Rayner, L., Hotopf, M., Kingsley, G. H., Norton, S., Scott, D. L., & Steer, S. (2014). The impact of rheuamtoid arthritis on quality-of-life assessed using the SF-36: A systematic review and meta-analysis. *Seminars in Arthritis and Rheuamtism*, 44, 123-30.

Mayoux-Benhamou, M. A. (2006). Fatigue and rheumatoid arthritis. *Annales de réadaptation et de médecine physique: Revue scientifique de la Société francaise de rééducation fonctionnelle de réadaptation et de médecine physique*, 49, 301-4.

Michielsen, H. J., De Vries, J. & Van Heck, G. L. (2003). In search of personality and temperament predictors of chronic fatigue: A prospective study. *Personality and Individual Differences*, 35, 1073-1087.

Moher, D., Liberati, A., Tetzlaff, J., Altmann, D. G, & the PRISMA group. (2009). The PRISMA group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA statement. *British Medical Journal,* 339, b2535.

*Neame, R. & Hammond, A. (2005). Beliefs about medications: A questionnaire survey of people with rheumatoid arthritis. *Rheumatology,* 44, 762-767.

Neuberger, G. B. (2003). Measures of fatigue: The Fatigue Questionnaire, Fatigue Severity Scale, Multidimensional Assessment of Fatigue Scale, and Short-Form-36 Vitality (Energy/Fatigue) Subscale of the Short Form Health Survey. *Arthritis Care & Research*, 49, S175-183.

*Nicklin, J., Cramp, F., Kirwan, J., Greenwood, R., Urban, M., & Hewlett, S. (2010). Measuring fatigue in Rheumatoid Arthritis: A cross-sectional study to evaluate the Bristol Rheumatoid Arthritis Fatigue Multi-Dimensional Questionnaire, Visual Analog Scales, and Numerical Rating Scales. *Arthritis Care & Research*, 62, 1559-1568.

Nikolaus, S., Bode, C., Taal, E., & van de Laar, M. A. F. J. (2013). Fatigue and factors related to fatigue in Rheumatoid Arthritis: A systematic review. *Arthritis Care & Research*, 65, 1128-46.

Pawlikowska, T., Chalder, T., Hirsch, S. R., Wallace, P., Wright, D. L., & Wessely, S. C. (1994). Population based study of fatigue and psychological distress. *British Medical Journal*, 308, 763-6.

Parkerson, G. R., Jr., Broadhead, W. E. & Tse, C. K. (1991). Validation of the Duke Social Support and Stress Scale. *Family Medicine*, 23, 357-360.

*Pollard, L. C., Choy, E. H., Gonzalez, J., Khoshaba B. & Scott, D. L. (2006). Fatigue in rheumatoid arthritis reflects pain, not disease activity. *Rheumatology,* 45, 885-889.

Repping-Wuts, H., Fransen, J., van Achterberg, T., Bleijenberg, G., van Riel, P. (2007). Persistent severe fatigue in patients with rheumatoid arthritis. *Journal of Clinical Nursing,* 16, 377-83.

Revenson, T. A., Schiaffino, K. M., Majerovitz, D. S., & Gibofsky, A. (1991). Social support as a double-edged sword: The relation of positive and problematic support to depression among rheumatoid arthritis patients. *Social Science & Medicine,* 33, 807-813.

*Rezvani, A., Demir, S. E., Ozaras, N., Poyraz, E., & Guneser, M. (2012). The factors associated with depression, anxiety and illness perceptions in patients with rheumatoid arthritis. *Rheumatology* 51, i25.

*Riemsma, R. P., Rasker, J. J., Taal, E., Griep, E. N., Wouters, J. M. G. W., & Wiegman, O. (1998). Fatigue in rheumatoid arthritis: The role of self-efficacy and problematic social support. *British Journal of Rheumatology*, 37, 1042-1043.

Robins, L. N. & Helzer, J. E. (1985). Diagnostic Interview Schedule (DIS) version III-A. St. Louis: Department of Psychiatry, Washington University School of Medicine.

Rothwell, P. M. (2005). External validity of randomised controlled trials: "To whom to the results apply?" *Lancet*, 365, 82-93.

*Rupp, I., Boshuizen, H. C., Jacobi, C. E., Dinant, H. J., & van den Bos, G. A. M. (2004). Impact of fatigue on health-related quality of life in rheumatoid arthritis. *Arthritis & Rheumatism*, 51, 578-585.

Sharpe, L., Sensky, T., Timberlake, N., Ryan, B., Brewin, C. R., & Allard, S. (2001). A blind, randomized, controlled trial of cognitive-behavioural intervention for patients with recent onset rheumatoid arthritis: Preventing psychological and physical morbidity. *Pain*, 89, 275-283.

*Stebbings, S., Herbison, P., Doyle, T. C. H., Treharne, G. J. & Highton, J. (2010). A comparison of fatigue correlates in rheumatoid arthritis and osteoarthritis: Disparity in

associations with disability, anxiety and sleep disturbance. *Rheumatology*, 49, 361-367.

*Stone, A. Broderick, A., J. E., Porter, L. S. & Kaell, A. T. (1997). The experience of rheumatoid arthritis pain and fatigue: Examining momentary reports and correlates over one week. *Arthritis Care & Research*, 10, 185-193.

Surawy, C., Hackmann, A., Hawton, K. & Sharpe, M. (1995). Chronic fatigue syndrome: A cognitive approach. *Behaviour Research and Therapy*, 33, 535-544.

Taal, E., Rasker, J. J., Seydel, E. R., & Wiegman, O. (1993). Health status, adherence with health recommendations, self-efficacy and social support in patients with rheumatoid arthritis. *Patient Education and Counseling*, 20, 63-76.

Tack, B. B. (1990). Fatigue in rheumatoid arthritis: Conditions, strategies, and consequences. *Arthritis & Rheumatism*, 3, 65-70.

Thoits, P. A. (2011). Mechanisms linking social ties and support to physical and mental thealth. *Journal of Health and Social Behavior*, 52, 145-161.

*Thyberg I, Dalström, O., Thyberg, M. (2009). Factors related to fatigue in women and men with eraly rheuamtoid arthritis: The Swedish TIRA study. *Journal of Rehabilitation Medicine*, 41, 904-912.

*Treharne, G. J., Kitas, G. D., Lyons, A. C. & Booth, D. A. (2005). Well-being in Rheumatoid Arthritis: The effects of disease duration and psychosocial factors. *Journal of Health Psychology*, 10, 457-474.

*Treharne, G. J., Lyons, A. C., Hale, E. D., Douglas, K. M. J., Goodchild, C. E., Booth, D. A. & Kitas, G. D. (2007). Sleep disruption frequency in rheumatoid arthritis: Perceived stress predicts poor outcome over one year. *Musculoskeletal Care*, 5, 51-64.

*Treharne, G., Lyons, A., Hale, E., Goodchild, C., Booth, D., & Kitas, G. (2008). Predictors of fatigue over 1 year among people with rheumatoid arthritis. *Psychology, Health & Medicine*, 13, 494-504.

*van Hoogmoed, D., Fransen, J., Bleijenberg G., & van Riel, P. (2010). Physical and psychosocial correlates of severe fatigue in rheumatoid arthritis. *Rheumatology*, 49, 1294-1302.

Ward, M. M. (1994). Are patient self-report measures of arthritis activity confounded by mood? A longitudinal study of patients with rheumatoid arthritis. *The Journal of Rheumatology*, 21, 1046-1050.

Ware, J. E. Jr., & Sherbourne, C. D. (1992). The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Medical Care*, 30, 473-483.

Weinman, J., Petrie, K. J., Moss-Morris, R. & Horne, R (1996). The illness perception questionnaire: A new method for assessing the cognitive representation of illness. *Psychology & Health*, 11, 431-445.

*Waltz, M. (2000). The disease process and utilization of health services in rheumatoid arthritis: The relative contributions of various markersof disease severity in explaining consumption patterns. *Arthritis Care & Research*, 13, 74-88.

*Wolfe, F., Hawley, D. J. & Wilson, K. (1996). The prevalence and meaning of fatigue in rheumatic disease. *The Journal of Rheumatology*, 23, 1407-1417.

*Wolfe, F. & Michaud, K. (2004). Fatigue, rheumatoid arthritis, and anti-tumor necrosis factor therapy: An investigation in 24,831 patients. *Journal of Rheumatology*, 31, 2115-2120.